



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/425	A1	(11) International Publication Number: WO 99/25346 (43) International Publication Date: 27 May 1999 (27.05.99)
(21) International Application Number: PCT/JP98/05178 (22) International Filing Date: 18 November 1998 (18.11.98) (30) Priority Data: 9/317926 19 November 1997 (19.11.97) JP (71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): MATSUI, Junji [JP/JP]; 1-11-1109, Esakacho 2-chome, Suita-shi, Osaka 564-0063 (JP). TARUI, Naoki [JP/JP]; 6-1, Mitsugarasu 1-chome, Nara-shi, Nara 631-0061 (JP). MOMOSE, Yu [JP/JP]; 2-1-213, Sumiregaoka 3-chome, Takarazuka-shi, Hyogo 665-0847 (JP). NARUO, Ken-ichi [JP/JP]; 22-16, Yokoyama-cho, Sanda-shi, Hyogo 669-1534 (JP). (74) Agents: ASAHINA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-0024 (JP).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: NOVEL APOPTOSIS INHIBITORS <div style="text-align: center;"> </div> <div style="text-align: right;">(1)</div>		
(57) Abstract <p>An apoptosis inhibitor which comprises a compound of formula (1) wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula: -CO-, -CH(OH)- or -NR³- where R³ represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R¹ represents hydrogen or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R¹; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond; or a salt thereof, or a compound having an insulin sensitivity enhancing activity.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NOVEL APOPTOSIS INHIBITORS
DESCRIPTION

TECHNICAL FIELD

5 The present invention relates to an apoptosis inhibitor which is useful as an agent for prophylaxis and treatment of a disease mediated by promotion of apoptosis.

BACKGROUND ART

10 Apoptosis means a physiological and active death of cells, abnormality of which is known to be closely related with occurrence of various diseases [Rinshou Byouri, vol.45, No.7, pp.603-605 (1997); Igaku no Ayumi, vol.178, No.10, pp.712-716 (1996)].

15 As compounds having an apoptosis inhibitory activity, there are known, for instance, (1-heteroazolyl-1-heterocyclyl)alkane derivatives (JP-A H8(1996)-512312), (3S, 4aR, 6R, 8aR)-6-[2-(1H-tetrazol-5-yl)-ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid (European Journal of Pharmacology, vol.314, pp.249-254 (1996)) and the like.

20 Saishin igaku, vol.52, No.6, pp.95-102 (1997), especially at page 100 describes "thiazolidines will, probably via PPAR γ activities, promote differentiation
25 from preadipocytes to adipocytes, remarkably increase the number of small adipocytes, and decrease the number of large adipocytes (apoptosis ??)", "thiazolidine derivatives affecting fatty tissues show remarkable effects to this types of insulin resistance", and shows "a mechanism of
30 thiazolidine derivatives in changes of fatty tissues and improvement of insulin resistance (hypothesis)". However, these do not relate to an apoptosis inhibitory activity.

35 Drugs showing an apoptosis inhibitory activity can be used as an agent for prophylaxis and treatment of diseases which are thought to be mediated by promotion of apoptosis,

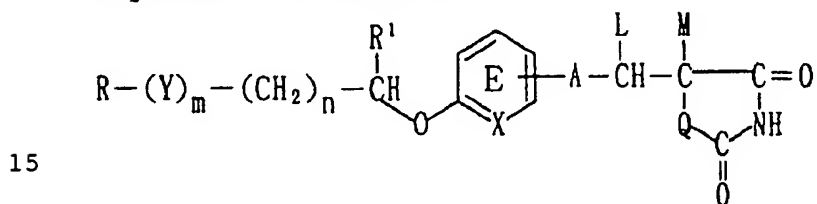
such as viral diseases, neurodegenerative diseases, myelodysplasia, ischemic diseases and hepatic diseases.

Therefore, development of such new types of drug is desired.

5

DISCLOSURE OF INVENTION

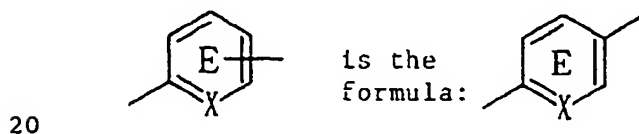
The inventors of the present invention, after various research about compounds having an apoptosis inhibitory activity, found, for the first time, that compounds having
10 an insulin sensitivity enhancing activity, especially the compound of the formula:



wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula: -CO-,
20 -CH(OH)- or -NR³- where R³ represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R¹ represents hydrogen or an alkyl group;
25 ring E may have further 1 to 4 substituents, which may form a ring in combination with R¹; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond; or a salt thereof; which are characterized by azolidine and a particular side chain thereto,
30 unexpectedly showed an excellent apoptosis inhibitory activity based on the characteristic chemical structure, and that it was useful as an agent for prophylaxis and treatment of diseases which are thought to be mediated by promotion of apoptosis. Based on this finding, the present
35 invention has been completed.

The present invention relates to

- (1) An apoptosis inhibitor which comprises a compound represented by the formula (I);
- (2) An apoptosis inhibitor according to the above (1), wherein the heterocyclic group represented by R is a 5- to 7-membered monocyclic and heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen in addition to carbon as ring members or its condensed heterocyclic group;
- (3) An apoptosis inhibitor according to the above (1), wherein R represents a heterocyclic group that may be substituted;
- (4) An apoptosis inhibitor according to the above (3), wherein the heterocyclic group is pyridyl, oxazolyl, thiazolyl or triazolyl;
- (5) An apoptosis inhibitor according to the above (1), wherein the partial structural formula:



- (6) An apoptosis inhibitor according to the above (1), wherein X represents CH;
- (7) An apoptosis inhibitor according to the above (1), wherein R¹ represents hydrogen;
- (8) An apoptosis inhibitor according to the above (1), wherein L and M respectively represent hydrogen;
- (9) An apoptosis inhibitor which comprises a compound having an insulin sensitivity enhancing activity;
- (10) An apoptosis inhibitor according to the above (1), which is an agent for prophylaxis or treatment of a neurodegenerative disease;
- (11) An apoptosis inhibitor according to the above (1), which comprises pioglitazone or its salt;
- (12) An apoptosis inhibitor according to the above (1), which comprises troglitazone or its salt;
- (13) An apoptosis inhibitor according to the above (1),

which comprises rosiglitazone or its salt;

(14) Method for inhibiting apoptosis in a mammal, which comprises administering to said mammal an effective amount of a compound or a salt as defined in the above (1);

5 (15) Method for treating or preventing a disease mediated by promotion of apoptosis in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound or a salt as defined in the above (1);

(16) Use of a compound or a salt as defined in the above
10 (1) for the manufacture of an agent for prophylaxis or treatment of a disease mediated by promotion of apoptosis;

(17) Method for inhibiting apoptosis in a mammal, which comprises administering to said mammal an effective amount of a compound having an insulin sensitivity enhancing
15 activity;

(18) Method for treating or preventing a disease mediated by promotion of apoptosis in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound having an insulin sensitivity enhancing
20 activity; and

(19) Use of a compound having an insulin sensitivity enhancing activity for the manufacture of an agent for prophylaxis or treatment of a disease mediated by promotion of apoptosis.

25

The compound used in the present invention is not limited as long as it is a compound having an insulin sensitivity enhancing activity. Especially preferred is the compound represented by the formula (I) or salt thereof.

30 Substituents in the formula (I) are explained below.

Referring to the hydrocarbon group that may be substituted for R, the hydrocarbon group includes aliphatic hydrocarbon groups, alicyclic hydrocarbon groups,
35 alicyclic-aliphatic hydrocarbon groups, aromatic-aliphatic hydrocarbon groups, and aromatic hydrocarbon

groups. The number of carbon atoms constituting such hydrocarbon groups is preferably 1 to 14.

The aliphatic hydrocarbon group is preferably a C_{1-8} aliphatic hydrocarbon group. The aliphatic hydrocarbon group includes saturated C_{1-8} aliphatic hydrocarbon groups (e.g. alkyl groups) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, hexyl, isohexyl, heptyl, and octyl; and unsaturated C_{2-8} aliphatic hydrocarbon groups (e.g. alkenyl, alkadienyl, alkynyl, and alkadiynyl groups) such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl, and 1-octynyl.

The alicyclic hydrocarbon group is preferably a C_{3-7} alicyclic hydrocarbon group. The alicyclic hydrocarbon group includes saturated C_{3-7} alicyclic hydrocarbon groups (e.g. cycloalkyl groups) such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. and unsaturated C_{3-7} alicyclic hydrocarbon groups (e.g. cycloalkenyl groups and cycloalkadienyl groups) such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, and 2,4-cycloheptadienyl.

The alicyclic-aliphatic hydrocarbon group is a group consisting of the above-described alicyclic hydrocarbon group and aliphatic hydrocarbon group (e.g. cycloalkyl-alkyl and cycloalkenyl-alkyl groups) and is preferably a C_{4-} alicyclic-aliphatic hydrocarbon group. Specifically, the alicyclic-aliphatic hydrocarbon group includes cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl,

cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl, cycloheptylethyl, etc.

The aromatic-aliphatic hydrocarbon group is preferably a C_{7-13} aromatic-aliphatic hydrocarbon group (e.g. aralkyl and aryl-alkenyl groups). The aromatic-aliphatic hydrocarbon group includes C_{7-9} phenylalkyl such as benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl; C_{11-13} naphthylalkyl such as α -naphthylmethyl, α -naphthylethyl, β -naphthylmethyl, and β -naphthylethyl; C_{8-10} phenylalkenyl such as styryl and 4-phenyl-1,3-butadienyl; and C_{12-13} naphthylalkenyl such as 2-(2-naphthyl)vinyl.

The aromatic hydrocarbon group is preferably a C_{6-14} aromatic hydrocarbon group (e.g. aryl groups). The aromatic hydrocarbon group includes phenyl and naphthyl (α -naphthyl, β -naphthyl).

Referring to the formula (I), the heterocyclic group in a heterocyclic group that may be substituted for R is a 5- to 7-membered monocyclic and heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as ring members or its condensed heterocyclic group. The condensed heterocyclic group may for example be one consisting of such a 5- to 7-membered monocyclic and heterocyclic group and a 6-membered ring containing 1 or 2 nitrogen atoms, a benzene ring, or a 5-membered ring containing one sulfur atom.

Specifically the heterocyclic group includes 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyrazolyl, 4-pyrazolyl, isothiazolyl, isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-

oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, tetrazol-5-yl, benzimidazol-2-yl, indol-3-yl, 1H-indazol-3-yl, 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyridin-6-yl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 1H-imidazo[4,5-b]pyrazin-2-yl, benzopyranyl and 3,4-dihydrobenzopyran-2-yl. The preferred heterocyclic group is pyridyl, oxazolyl, thiazolyl, or triazolyl group.

Referring to the formula (I), the hydrocarbon group and heterocyclic group for R may respectively have 1 to 5, preferably 1 to 3 substituents at substitutable positions.

Such substituents include for example aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, aryl groups, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen, nitro, amino group that may be substituted, acyl group that may be substituted, hydroxy group that may be substituted, thiol group that may be substituted, and carboxyl group that may be esterified.

The aliphatic hydrocarbon group includes straight-chain or branched aliphatic hydrocarbon groups having 1 to 15 carbon atoms, such as alkyl groups, alkenyl groups, and alkynyl groups.

The preferred alkyl group is a C_{1-10} alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl, and decyl.

The preferred alkenyl group is a C_{2-10} alkenyl group, such as vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

The preferred alkynyl group is a C_{2-10} alkynyl group, such as ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-

butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

The alicyclic hydrocarbon group includes saturated and unsaturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms, such as cycloalkyl groups, cycloalkenyl groups, and cycloalkadienyl groups.

The preferred cycloalkyl group is a C_{3-10} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, and bicyclo[4.3.1]decyl.

The preferred cycloalkenyl group is a C_{3-10} cycloalkenyl group, such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, and 3-cyclohexen-1-yl.

The preferred cycloalkadienyl group is a C_{4-10} cycloalkadienyl group, such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl.

The term "aryl group" means a monocyclic or condensed polycyclic aromatic hydrocarbon group. As preferred examples, C_{6-14} aryl groups such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylene can be mentioned. Particularly preferred are phenyl, 1-naphthyl, and 2-naphthyl.

The preferred aromatic heterocyclic group includes 5- to 7-membered monocyclic aromatic heterocyclic groups containing 1 to 4 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as ring members, such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl; and bicyclic or tricyclic condensed aromatic heterocyclic groups containing 1 to 5 hetero-atoms selected from oxygen, sulfur, and nitrogen in addition to carbon as
5 ring members, such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl,
10 quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl,
15 pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, and 1,2,4-triazolo[4,3-b]pyridazinyl.

20 The preferred non-aromatic heterocyclic group includes oxiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidino, piperidino, morpholino, and
25 thiomorpholino.

The halogen includes fluorine, chlorine, bromine, and iodine, and is preferably fluorine or chlorine.

The amino group that may be substituted includes amino (-NH₂) that may be mono- or di-substituted by, for example,
30 C₁₋₁₀ alkyl groups, C₃₋₁₀ cycloalkyl groups, C₂₋₁₀ alkenyl groups, C₃₋₁₀ cycloalkenyl groups, C₁₋₁₃ acyl groups (e.g. C₂₋₁₀ alkanoyl groups, C₇₋₁₃ arylcarbonyl groups), or C₆₋₁₂ aryl groups. As examples of the substituted amino group, there can be mentioned methylamino, dimethylamino, ethylamino,
35 diethylamino, dibutylamino, diallylamino, cyclohexylamino, acetylamino, propionylamino,

benzoylamino, phenylamino, and N-methyl-N-phenylamino.

The acyl group in the acyl groups that may be substituted includes C₁₋₁₃ acyl groups. For example, formyl and groups formed between carbonyl and C₁₋₁₀ alkyl groups, C₃₋₁₀ cycloalkyl groups, C₂₋₁₀ alkenyl groups, C₃₋₁₀ cycloalkenyl groups, C₆₋₁₂ aryl groups, or aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl). The preferred acyl group includes acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, and nicotinoyl. The substituent in the substituted acyl groups includes C₁₋₃ alkyl, C₁₋₃ alkoxy groups, halogen (e.g. chlorine, fluorine, bromine, etc.), nitro, hydroxy, and amino.

Referring to the hydroxy group that may be substituted, the substituted hydroxy includes alkoxy, alkenyloxy, aralkyloxy, acyloxy, and aryloxy groups.

The preferred alkoxy group includes C₁₋₁₀ alkoxy groups, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy, and cyclohexyloxy.

The preferred alkenyloxy group includes C₂₋₁₀ alkenyloxy groups, such as allyloxy, crotyloxy, 2-pentenylloxy, 3-hexenylloxy, 2-cyclopentenylmethoxy, and 2-cyclohexenylmethoxy.

The preferred aralkyloxy group includes C₇₋₁₀ aralkyloxy groups, such as phenyl-C₁₋₄ alkyloxy (e.g. benzyloxy, phenethylloxy, etc.).

The preferred acyloxy group includes C₂₋₁₃ acyloxy groups, more preferably C₂₋₄ alkanoyloxy (e.g. acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.).

The preferred aryloxy group includes C₆₋₁₄ aryloxy groups, such as phenoxy, and naphthyloxy. This aryloxy

group may have 1 or 2 substituents such as halogen (e.g. chlorine, fluorine, bromine, etc.). The substituted aryloxy group includes 4-chlorophenoxy.

Referring to the thiol group that may be substituted,
5 the substituted thiol group includes alkylthio, cycloalkylthio, aralkylthio, and acylthio groups.

The preferred alkylthio group includes C_{1-10} alkylthio groups, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio,
10 t-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, and nonylthio.

The preferred cycloalkylthio group includes C_{3-10} cycloalkylthio groups such as cyclobutylthio, cyclopentylthio, and cyclohexylthio.

15 The preferred aralkylthio group includes C_{7-10} aralkylthio groups, such as phenyl- C_{1-4} alkylthio (e.g. benzylthio, phenethylthio, etc.).

The acylthio group is preferably a C_{2-13} acylthio group, more preferably a C_{2-4} alkanoylthio group (e.g. acetylthio,
20 propionylthio, butyrylthio, isobutyrylthio, etc.).

The carboxyl group that may be esterified includes alkoxycarbonyl, aralkyloxycarbonyl, and aryloxycarbonyl groups.

The preferred alkoxycarbonyl group includes C_{2-5}
25 alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and butoxycarbonyl.

The preferred aralkyloxycarbonyl group includes C_{8-10} aralkyloxycarbonyl groups, such as benzyloxycarbonyl.

The preferred aryloxycarbonyl group includes C_{7-15}
30 aryloxycarbonyl groups, such as phenoxycarbonyl, and p-tolyloxycarbonyl.

The preferred substituent on the hydrocarbon or heterocyclic group for R includes C_{1-10} alkyl groups, aromatic heterocyclic groups, and C_{6-14} aryl groups.
35 Particularly preferred is C_{1-3} alkyl, furyl, thienyl, benzofuranyl, phenyl, or naphthyl.

Referring to the formula (I), when the substituent on the hydrocarbon or heterocyclic group for R is an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group, or a non-aromatic heterocyclic group, this substituent may be further substituted by one or more, preferably 1 to 3 suitable substituents. As such substituents, there can be mentioned C₁₋₆ alkyl groups, C₂₋₆ alkenyl groups, C₂₋₆ alkynyl groups, C₃₋₇ cycloalkyl groups, C₆₋₁₄ aryl groups (e.g. phenyl, naphthyl, etc.), aromatic heterocyclic groups (e.g. thienyl, furyl, pyridyl, oxazolyl, thiazolyl, etc.), non-aromatic heterocyclic groups (e.g. tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidino, piperazino, etc.), C₇₋₉ aralkyl groups, amino, N-mono(C₁₋₄)alkylamino groups, N,N-di(C₁₋₄)alkylamino groups, C₂₋₈ acylamino groups (e.g. acetylamino, propionylamino, benzoylamino, etc.), amidino, C₂₋₈ acyl groups (e.g. C₂₋₈ alkanoyl groups, etc.), carbamoyl, N-mono(C₁₋₄)alkylcarbamoyl groups, N,N-di(C₁₋₄)alkylcarbamoyl groups, sulfamoyl, N-mono(C₁₋₄)alkylsulfamoyl groups, N,N-di(C₁₋₄)alkylsulfamoyl groups, carboxyl, C₂₋₈ alkoxycarbonyl groups, hydroxy, C₁₋₄ alkoxy groups, C₂₋₅ alkenyloxy groups, C₃₋₇ cycloalkyloxy groups, C₇₋₉ aralkyloxy groups, C₆₋₁₄ aryloxy groups (e.g. phenyloxy, naphthyloxy, etc.), mercapto, C₁₋₄ alkylthio groups, C₇₋₉ aralkylthio groups, C₆₋₁₄ arylthio groups (e.g. phenylthio, naphthylthio, etc.), sulfo, cyano, azido, nitro, nitroso, and halogen (e.g. fluorine, chlorine, bromine, iodine).

In the formula (I), R is preferably a heterocyclic group that may be substituted. More preferably, R is pyridyl, oxazolyl, thiazolyl, or triazolyl group, which may have 1 to 3 substituents selected from C₁₋₃ alkyl, furyl, thienyl, benzofuranyl, phenyl, and naphthyl.

Referring to the formula (I), Y represents -CO-, -CH(OH)- or -NR³-. Y is preferably -CH(OH)- or -NR³- and more

preferably $-NR^3-$. Referring to an alkyl group that may be substituted for R^3 , the alkyl group includes C_{1-4} alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and t-butyl. The substituent includes halogen
5 (e.g. fluorine, chlorine, bromine, iodine), C_{1-4} alkoxy groups (e.g. methoxy, ethoxy, propoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy), hydroxy, nitro, and C_{1-4} acyl groups (e.g. formyl, acetyl, propionyl, etc.). R^3 is preferably C_{1-4} alkyl groups, especially preferably methyl.

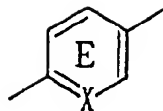
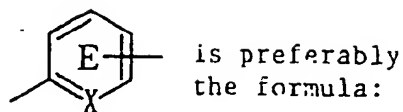
10 The symbol n represents 0, 1 or 2, and is preferably 0 or 1.

X represents CH or N, and is preferably CH.

Referring to the formula (I), A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to
15 7 carbon atoms. This aliphatic hydrocarbon group may be straight-chain or branched and may further be saturated or unsaturated. Thus, for example, $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_2-$, $-CH(C_2H_5)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, etc. can be mentioned for the saturated bivalent aliphatic
20 hydrocarbon group, while $-CH=CH-$, $-C(CH_3)=CH-$, $-CH=CH-CH_2-$, $-C(C_2H_5)=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-CH_2-$, $-CH=CH-CH=CH-CH_2-$, $-CH=CH-CH=CH-CH=CH-CH_2-$, etc. can be mentioned for the unsaturated bivalent aliphatic hydrocarbon group. The symbol A preferably represents a
25 chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 4 carbon atoms, which is preferably a saturated group. More preferably, A represents a chemical bond, $-CH_2-$, or $-(CH_2)_2-$. Still more preferably, A represents a chemical bond or $-(CH_2)_2-$.

30 The alkyl group for R^1 includes C_{1-4} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and t-butyl. R^1 represents preferably hydrogen or methyl, more preferably hydrogen.

35 Referring to the formula (I), the partial structural formula:

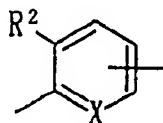
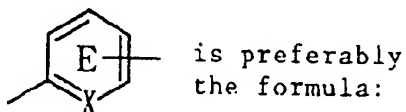


5 wherein each symbols has the same meanings as defined above.

Furthermore, ring E may optionally have 1 to 4
substituents at substitutable positions. Such
substituents include an alkyl group, a hydroxy group that
may be substituted, halogen, an acyl group that may be
10 substituted, nitro, and an amino group that may be
substituted. These substituents may be the same as the
substituents mentioned for the hydrocarbon or heterocyclic
group for R.

Ring E, namely the partial structural formula:

15



wherein R^2 represents hydrogen, an alkyl group, a hydroxy
20 group that may be substituted, halogen, an acyl group that
may be substituted, nitro, or an amino group that may be
substituted.

The alkyl group, hydroxy group that may be substituted,
halogen, acyl group that may be substituted, and amino group
25 that may be substituted, for R^2 , may each be the same as
the substituents mentioned for the hydrocarbon or
heterocyclic group for R. Preferably, R^2 is hydrogen,
hydroxy group that may be substituted, or halogen. More
preferably, R^2 is hydrogen, a C_{1-4} alkoxy group, or halogen.

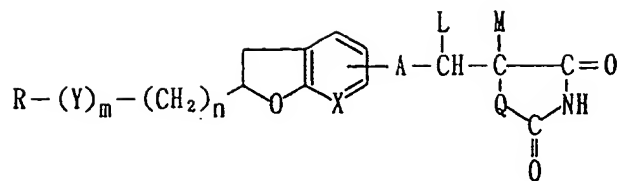
30

Referring to the formula (I), compounds in which a
substituent on Ring E and R^1 are combined to form a ring
include compounds represented by the following formulae.

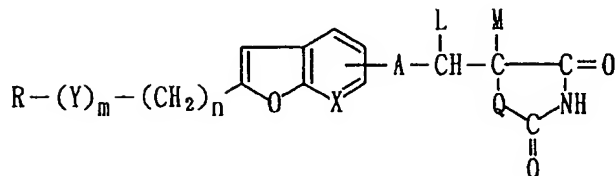
35

15

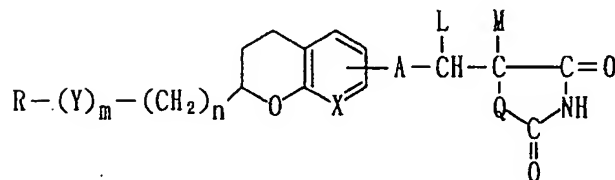
5



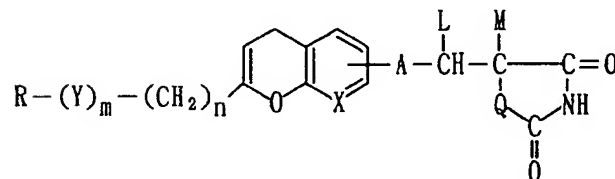
10



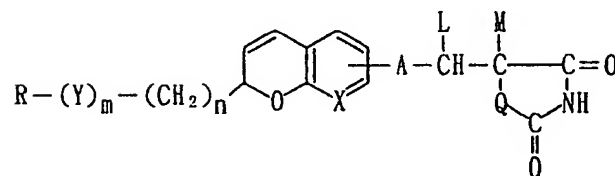
15



20



25

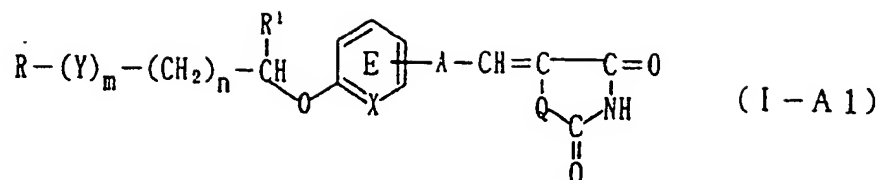


30 wherein each symbols has the same meanings as defined above.

L and M respectively represent hydrogen or may be combined with each other to form a chemical bond, and preferably they are hydrogen.

Referring to the formula (I), the compound in which
 35 L and M are combined with each other to form a chemical bond:

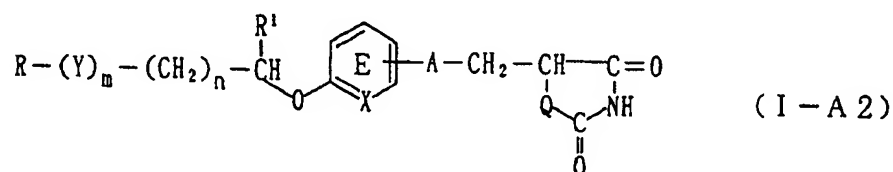
16



5

wherein each symbols has the same meanings as defined above, may exist as (E)- and (Z)- isomers, owing to the double bond at 5-position of the azolidinedione ring.

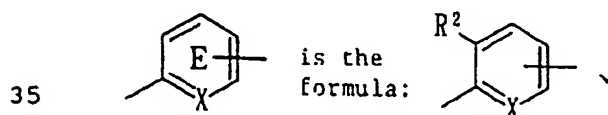
10 The compound in which L and M respectively represent hydrogen:



15

wherein each symbols has the meanings as defined above, may exist as optical isomers, i.e. (R)- and (S)-forms, with respect to the asymmetric carbon at 5-position of the azolidinedione ring. This compound includes those optically active compounds, i.e. (R)- and (S)-forms, as well as the racemic form.

The preferred compound represented by the formula (I) includes the compound in which R represents pyridyl, oxazolyl, thiazolyl, or triazolyl group, optionally having 1 to 3 substituents selected from the group consisting of C₁-, alkyl, furyl, benzofuranyl, thienyl, phenyl, and naphthyl; Y represents -CH(OH)- or -NR³- wherein R³ is methyl; n is 0 or 1; A represents a chemical bond or -(CH₂)₂-; R¹ represents hydrogen or methyl; ring E, namely the partial structural formula:



wherein R² is hydrogen, a C₁-, alkoxy group or halogen; and L and M respectively represent hydrogen.

As preferred species of the compound represented by the formula (I), the following compounds are mentioned.

- 5 1) 5-[3-[3-fluoro-4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione;
- 2) 5-[3-[4-[2-[5-methyl-2-(2-naphthyl)-4-oxazolylethoxy]phenyl]propyl]-2,4-oxazolidinedione;
- 3) 5-[3-[4-[2-(benzo[b]furanyl)-5-methyl-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione;
- 10 4) 5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione;
- 5) 5-[3-[4-[5-methyl-2-(2-naphthyl)-4-oxazolylmethoxy]phenyl]propyl]-2,4-oxazolidinedione;
- 15 6) 5-[3-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)phenyl]propyl]-2,4-oxazolidinedione;
- 7) 5-[2-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridylmethyl]-2,4-thiazolidinedione;
- 8) 5-[4-[2-(1-methyl-5-phenyl-1,2,4-triazol-3-yl)ethoxy]benzyl]-2,4-thiazolidinedione;
- 20 9) 5-[3-[2-(5-methyl-2-phenyl-4-oxazolylmethoxy)-5-pyridyl]propyl]-2,4-thiazolidinedione;
- 10) 5-[2-(5-methyl-2-phenyl-4-oxazolylmethyl)-5-benzofuranylmethyl]-2,4-oxazolidinedione;
- 25 11) 5-[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione;
- 12) 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione;
- 13) 5-[4-[2-(methyl-2-pyridylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: rosiglitazone);
- 30 14) (R)-(+)-5-[3-[4-[2-(2-furyl)-5-methyl-4-oxazolylmethoxy]-3-methoxyphenyl]propyl]-2,4-oxazolidinedione;
- 35 15) 5-[2-[2-(5-isopropyl-2-phenyl-4-oxazolyl)ethoxy]-5-pyridylmethyl]-2,4-thiazolidinedione;

- 16) 5-[3-[3-methoxy-4-[1-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propyl]-2,4-oxazolidinedione;
17) 5-[4-[2-[5-methyl-2-(2-naphthyl)-4-oxazolyl)ethoxy]benzyl]-2,4-oxazolidinedione;
5 18) 5-[2-[4-[2-[5-methyl-2-(2-naphthyl)-4-oxazolyl)ethoxy]phenyl]ethyl]-2,4-oxazolidinedione;
19) 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (generic name: pioglitazone);
20) 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-
10 2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (generic name: troglitazone).

The above 1) to 20) represent compound Nos. Hereafter, these compounds are sometimes simply referred to as compound No.1, compound No.2, and the like.

- 15 Among the above compounds, compound Nos. 13, 14, 19 and 20 are preferred, and compound Nos.13, 19 and 20 are particularly preferred.

- The compound represented by the formula (I) (hereafter simply referred to as compound (I)) has an acidic group or
20 a basic group in a molecule, and can form a basic salt or an acid-addition salt. The salt of compound (I) is preferably a pharmacologically acceptable salt, which includes salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids,
25 and salts with basic or acidic amino acids.

The preferred salt with an inorganic base includes alkali metal salts such as sodium salt, potassium salt, etc.; alkaline earth metal salts such as calcium salt, magnesium salt, etc.; aluminum salt, and ammonium salts.

- 30 The preferred salt with an organic base includes salts with tertiary amines such as trimethylamine, triethylamine, pyridine, picoline, triethanolamine, etc.; salts with secondary amines such as diethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.; and salts with
35 ethanolamine.

The preferred salt with an inorganic acid includes

salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

The preferred salt with an organic acid includes salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

The preferred salt with a basic amino acid includes salts with arginine, lysine, ornithine, etc. The preferred salt with an acidic amino acid includes salts with aspartic acid, glutamic acid, etc.

The most preferred of all the above-mentioned salts is hydrochloride, sodium salt or potassium salt.

The compound having an insulin sensitivity enhancing activity, for example, the compound (I) or a salt thereof, etc. can be produced in accordance with methods described in JP-A S55(1980)-22636 (EP-A-8203), JP-A S60(1985)-208980 (EP-A-155845), JP-A S61(1986)-286376 (EP-A-208420), JP-A S61(1986)-085372 (EP-A-177353), JP-A S61(1986)-267580 (EP-A-193256), JP-A H5(1993)-86057 (WO-A-9218501), JP-A H7(1995)-82269 (EP-A-605228), JP-A H7(1995)-101945 (EP-A-612743), EP-A-643050, EP-A-710659 (JP-A H9(1997)-194467), etc, or methods analogous thereto.

The compound having an insulin sensitivity enhancing activity which is used in the present invention is not limited as long as it is a compound which restores the impaired insulin receptor function to deblock insulin resistance and consequently enhances insulin sensitivity.

Such compound includes the above-described compound represented by the formula (I) or salt thereof.

The compound having an insulin sensitivity enhancing activity other than the above-described one includes, for example,

5-[[[3,4-dihydro-2-(phenylmethyl)-2H-1-benzopyran-6-yl]methyl]-2,4-thiazolidinedione (generic name:

- englitazone) or its sodium salt;
5-[[4-[3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl]phenyl]methyl]-2,4-thiazolidinedione (generic name: darglitazone/CP-86325) or its sodium salt;
5 5-(2-naphthalenylsulfonyl)-2,4-thiazolidinedione (AY-31637);
4-[(2-naphthalenyl)methyl]-3H-1,2,3,5-oxathiadiazol-2-oxide (AY-30711);
5-[6-(2-fluorobenzyloxy)naphthalene-2-ylmethyl]-2,4-
10 thiazolidinedione (MCC-555);
5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-[4-(trifluoromethyl)benzyl]benzamide (KRP-297);
(Z)-1,4-bis-4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-yl)methyl]phenoxybut-2-ene (YM440);
15 4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione (JTT-501).

An apoptosis inhibitory activity is evaluated, for instance, by adding a test compound to a system in which
20 apoptosis is caused, determining an apoptosis activity, and calculating an inhibitory ratio of the apoptosis activity. Methods for determining the apoptosis activity includes 1) a method which comprises inducing apoptosis by adding actinomycin D to cells, and quantitating DNA ladders of
25 cells [M. Hermann et al., Nucleic Acids Research, vol.22, p.5506 (1994); Y. A. Ioannou and F. W. Chen, Nucleic Acids Research, vol.24, p.992 (1996)]; 2) a method which comprises adding TNF- α to cells, and determining the cell death [Meneki Jikken Sousahou II, edited by S. Migita, S.
30 Konda, T. Honjyo, and T. Hamaoka, Nankoudou, pp.861-871 (1995)]; and the like.

As the apoptosis inhibitor of the present invention, "the compound having an insulin sensitivity enhancing
35 activity", for example, "the compound (I) or salt thereof" as such can be used. Usually, the apoptosis inhibitor can

be produced in accordance with a per se known means as a method for producing a pharmaceutical composition by using "the compound having an insulin sensitivity enhancing activity", for example, "the compound (I) or salt thereof" together with pharmaceutically acceptable carriers, and the like. Specifically, the apoptosis inhibitor is obtained by admixing the compound (I) or salt thereof with carriers in a conventional manner, and may be used in the form of a pharmaceutical composition.

10

As the pharmaceutically acceptable carrier, a variety of organic and inorganic carriers in common use as raw materials for pharmaceutical preparations are employed.

The carrier is formulated in the form of the excipient, lubricant, binder, and disintegrator for a solid dosage form; and the solvent, solubilizer, suspending agent, isotonizing agent, buffering agent and local analgesic for a liquid dosage form. When necessary, pharmaceutical additives such as the preservative, antioxidant, coloring agent, sweetener, etc. can also be used.

20

The preferred excipient includes lactose, sucrose, D-mannitol, xylitol, sorbitol, erythritol, starch, crystalline cellulose, light silicic anhydride, etc.

The preferred lubricant includes magnesium stearate, calcium stearate, talc, colloidal silica, etc.

25

The preferred binder includes pregelatinized starch, methyl cellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, etc.

30

The preferred disintegrator includes starch, carboxymethylcellulose, low-substituted hydroxypropylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, etc.

The preferred solvent includes water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, tricaprylin, etc.

35

The preferred solubilizer includes polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

5 The preferred suspending agent includes surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate, etc.; and hydrophilic polymers such as polyvinyl alcohol,
10 polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

The preferred isotonizing agent includes sodium chloride, glycerin, D-mannitol, etc.

15 The preferred buffering agent includes buffer solutions such as phosphate, acetate, carbonate, citrate, etc.

The preferred local anesthetic includes benzyl alcohol, etc.

20 The preferred antiseptic includes p-hydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

The preferred antioxidant includes salts of sulfurous acid, ascorbic acid, etc.

25 The content of "the compound having an insulin sensitivity enhancing activity" or "the compound (I) or salt thereof" in the apoptosis inhibitor of the present invention is about 5 to about 100 weight %, preferably about 10 to about 80 weight %.

30 The apoptosis inhibitor of the present invention can be manufactured by conventional methods in the pharmaceutical preparation techniques, for example methods described in the Japanese Pharmacopoeia (e.g., Thirteenth Edition).

35 Examples of dosage forms of the apoptosis inhibitor of the present invention include oral dosage forms such as

tablets, capsules (inclusive of soft capsules and microcapsules), powders, granules, and syrups; and non-oral dosage forms such as injections, suppositories, pellets, and drip infusions. These dosage forms are low in the toxic potential, and can be safely administered either orally or non-orally.

The apoptosis inhibitor of the present invention can be used as an agent for prophylaxis and treatment of a disease mediated by promotion of apoptosis in mammals (e.g., man, mouse, rat, rabbit, dog, cat, bovine, equine, swine, monkey, etc.).

Examples of such disease includes viral diseases such as AIDS and fulminant hepatitis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa and cerebellar degeneration; myelodysplasia such as aplastic anemia; ischemic diseases such as myocardial infarction and stroke; hepatic diseases such as alcoholic hepatitis, hepatitis B and hepatitis C; joint-diseases such as osteoarthritis; atherosclerosis; and etc. The apoptosis inhibitor of the present invention is especially preferably used as an agent for prophylaxis or treatment of a neurodegenerative disease.

The dosage of the apoptosis inhibitor of the present invention differs depending on the subject, route of administration, clinical condition, etc. For oral administration to an adult patient suffering from a neurodegenerative disease, for instance, the usual unit dose is about 0.1 mg/kg to about 30 mg/kg, preferably about 2 mg/kg to about 20 mg/kg, as an active ingredient, "the compound having an insulin sensitivity enhancing activity", for instance, "the compound (I) or salt thereof". This dose is preferably administered once to 3 times a day.

BEST MODE FOR CARRYING OUT THE INVENTION

The following examples and test examples are intended to describe the present invention in further detail and should by no means be construed as defining the scope of the invention.

5 Example 1

A fluidized-bed granulating and drying machine (produced by Powerex, Japan) was charged with 2479.5 g of hydrochloride of Compound No.19 (2250 g in terms of Compound No.19), 13930.5 g of lactose and 540 g of
10 carboxymethylcellulose calcium (carmellose calcium), followed by mixing at the preheating temperature and spraying 7500 g of an aqueous solution containing 450 g of hydroxypropylcellulose to yield granules. 16820 g of the granules were processed with cutter-mill (produced by Showa
15 Kagaku Kikai Kousakusho, Japan) to yield milled granules. 16530 g of the milled granules, 513 g of carmellose calcium and 57 g of magnesium stearate were mixed to yield lubricated powders by using tumbling mixer (produced by Showa Kagaku Kikai Kousakusho, Japan). 16800 g of the
20 lubricated powders were tabletted by using tableting machine (produced by Kikusui Seisakusho, Japan) to yield 140000 tablets having the following composition and each containing 15 mg of Compound No. 19.

Composition per tablet (Unit: mg):

25	1) Hydrochloride of Compound No.19	16.53
	2) Lactose	92.87
	3) Carmellose calcium	7.2
	4) Hydroxypropylcellulose	3.0
	5) Magnesium stearate	0.4
30		Total: 120.0

Example 2

In substantially the same manner as in Example 1, 140000 tablets having the following composition and each
35 containing 30 mg of Compound No.19 were obtained.
Composition per tablet (Unit: mg):

	1) Hydrochloride of Compound No.19	33.06
	2) Lactose	76.34
	3) Carmellose calcium	7.2
	4) Hydroxypropylcellulose	3.0
5	<u>5) Magnesium stearate</u>	<u>0.4</u>
Total: 120.0		

Example 3

In substantially the same manner as in Example 2,
10 140000 tablets having the following composition and each
containing 45 mg of Compound No.19 were obtained.

Composition per tablet (Unit: mg):

	1) Hydrochloride of Compound No.19	49.59
	2) Lactose	114.51
15	3) Carmellose calcium	10.8
	4) Hydroxypropylcellulose	4.5
	<u>5) Magnesium stearate</u>	<u>0.6</u>
Total: 180.0		

20 Test Example 1

Apoptosis (cell death) was induced by adding TNF-
 α to cells. The inhibitory activity of a test compound to
this apoptosis was determined by using known dexamethasone
having an apoptosis inhibitory activity as the standard.

25 Namely, 25 μ l of a culture medium (PRMI-1640,
produced by Nikken Seibutsu Igaku Kenkyusho, Japan)
(containing 10 weight % of fetal bovine serum) was added
to each wells of a 96-well microplate. Then, added was 2
 μ l of a solution prepared by 20 volume fold dilution of
30 dimethylformamide (in the case of Compound No. 16) or
dimethylsulfoxide (in the case of Compound Nos. 2, 4, 6,
8, 13) solution of a test compound (concentration of the
test compound: 1mM) with the above culture medium.

Subsequently, 25 μ l of a solution prepared by
35 dissolving TNF- α (Genzyme, USA)(40 ng/ml culture medium)
in the above culture medium, and 50 μ l of a suspension (2

X 10^5 cells/ml) prepared by suspending mouse fibroblast (L929 cells, IFO 50409) in the above culture medium were added, and then cells were cultivated for 72 hours at 37 °C in the presence of 5 % carbon dioxide in air. The final
5 concentration of the test compound during cultivation was 1 μ M.

After cultivation, the culture medium was removed from wells by aspiration, and 50 μ l of a 5%(w/v) crystal violet/70%(v/v) methanol solution was added to each wells
10 to pigment living cells. Then, wells were washed and dried.

The apoptosis inhibitory activity of the test compound was obtained by determining the optical density by using an absorptiometer [Microplate Reader Model 450, produced by Bio-Rad] at the wavelengths of 570 nm.

15 While, the apoptosis inhibitory activity of dexamethasone was obtained in the same manner as above except that the above test compound (final concentration: 1 μ M) was replaced by dexamethasone (final concentration: 1.1 μ M).

20 Then, the apoptosis inhibitory activity of each test compounds (final concentration: 1 μ M) was calculated when the apoptosis inhibitory activity of dexamethasone (final concentration: 1.1 μ M) was 100.

The results are shown in Table 1.

25 Table 1. Apoptosis inhibitory activity (%)

Test compound	Apoptosis inhibitory activity (%)
Compound No. 2	70
Compound No. 4	74
30 Compound No. 6	70
Compound No. 8	70
Compound No. 13	92
Compound No. 16	71

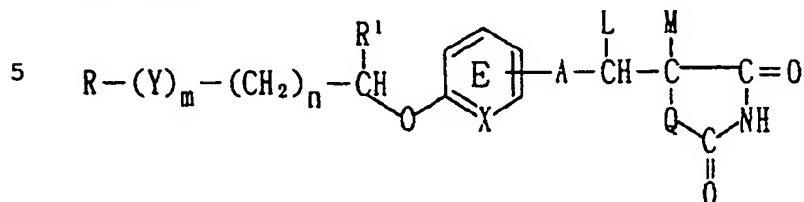
It is apparent from Table 1 that the compound (I) used
35 in the present invention inhibited apoptosis.

Industrial Applicability

The apoptosis inhibitor of the present invention shows an excellent apoptosis inhibitory activity, and is useful as an agent for prophylaxis and treatment of diseases
5 mediated by promotion of apoptosis, such as viral diseases, neurodegenerative diseases, myelodysplasia, ischemic diseases and hepatic diseases.

CLAIMS

1. An apoptosis inhibitor which comprises a compound of the formula:



wherein R represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Y represents a group of the formula: -CO-, -CH(OH)- or -NR³- where R³ represents an alkyl group that may be substituted; m is 0 or 1; n is 0, 1 or 2; X represents CH or N; A represents a chemical bond or a bivalent aliphatic hydrocarbon group having 1 to 7 carbon atoms; Q represents oxygen or sulfur; R¹ represents hydrogen or an alkyl group; ring E may have further 1 to 4 substituents, which may form a ring in combination with R¹; L and M respectively represent hydrogen or may be combined with each other to form a chemical bond; or a salt thereof.

2. An apoptosis inhibitor according to claim 1, wherein the heterocyclic group represented by R is a 5- to 7-membered monocyclic and heterocyclic group containing 1 to 4 hetero-atoms selected from oxygen, sulfur and nitrogen in addition to carbon as ring members or its condensed heterocyclic group.

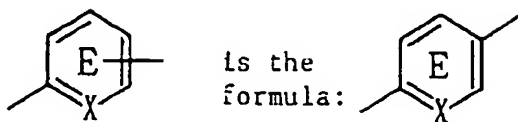
3. An apoptosis inhibitor according to claim 1, wherein R represents a heterocyclic group that may be substituted.

4. An apoptosis inhibitor according to claim 3, wherein the heterocyclic group is pyridyl, oxazolyl, thiazolyl or triazolyl.

35

5. An apoptosis inhibitor according to claim 1, wherein

the partial structural formula:



6. An apoptosis inhibitor according to claim 1, wherein X represents CH.
7. An apoptosis inhibitor according to claim 1, wherein R¹ represents hydrogen.
- 10 8. An apoptosis inhibitor according to claim 1, wherein L and M respectively represent hydrogen.
- 15 9. An apoptosis inhibitor which comprises a compound having an insulin sensitivity enhancing activity.
10. An apoptosis inhibitor according to claim 1, which is an agent for prophylaxis or treatment of a
- 20 neurodegenerative disease.
11. An apoptosis inhibitor according to claim 1, which comprises pioglitazone or its salt.
- 25 12. An apoptosis inhibitor according to claim 1, which comprises troglitazone or its salt.
13. An apoptosis inhibitor according to claim 1, which comprises rosiglitazone or its salt.
- 30 14. Method for inhibiting apoptosis in a mammal, which comprises administering to said mammal an effective amount of a compound or a salt as defined in claim 1.
- 35 15. Method for treating or preventing a disease mediated by promotion of apoptosis in a mammal in need thereof, which

comprises administering to said mammal an effective amount of a compound or a salt as defined in claim 1.

16. Use of a compound or a salt as defined in claim 1 for
5 the manufacture of an agent for prophylaxis or treatment of a disease mediated by promotion of apoptosis.

17. Method for inhibiting apoptosis in a mammal, which
comprises administering to said mammal an effective amount
10 of a compound having an insulin sensitivity enhancing activity.

18. Method for treating or preventing a disease mediated
by promotion of apoptosis in a mammal in need thereof, which
15 comprises administering to said mammal an effective amount of a compound having an insulin sensitivity enhancing activity.

19. Use of a compound having an insulin sensitivity
20 enhancing activity for the manufacture of an agent for prophylaxis or treatment of a disease mediated by promotion of apoptosis.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/05178

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 753 298 A (SANKYO CO) 15 January 1997 *cf. abstract, page 2, lines 1-11* ---	1-19
X	US 5 663 389 A (ROSINI GOFFREDO ET AL) 2 September 1997 *cf. abstract, col. 8, lines 3-25, col. 11, lines 52-54, and col. 13, lines 9-14* ---	1-19
X	US 5 457 109 A (ANTONUCCI TAMMY ET AL) 10 October 1995 *cf. abstract, col. 3, lines 54-58, col. 15, lines 14-51 and col. 18, example 1* ---	1-19
X	US 5 602 133 A (ANTONUCCI TAMMY ET AL) 11 February 1997 *cf. abstract, col. 15, lines 8-14, col. 17, last para. (example 1) and col. 19, lines 21-30 --- -/-	1-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 March 1999

Date of mailing of the international search report

23/03/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Stoltner, A

INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/JP 98/05178

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 9804 Derwent Publications Ltd., London, GB; Class B03, AN 98-037009 XP002095772 & JP 09 291031 A (YAMANOUCHI PHARM CO LTD) , 11 November 1997 see abstract</p>	1-19
X	<p>NAGASAKA Y., KAKU K., ET AL.: "The new oral hypoglycemic agent CS-045, inhibits the lipid peroxidation of human plasma low density lipoprotein in vitro" BIOCHEMICAL PHARMACOLOGY, vol. 50, no. 7, 28 September 1995, pages 1109-1111, XP002095771 * cf. abstract and page 1109, right col. bridging with page 1110, "Results and Discussion"*</p>	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/05178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0753298 A	15-01-1997	AU 5626196 A	16-01-1997
		CA 2180296 A	04-01-1997
		CN 1148492 A	30-04-1997
		CZ 9601982 A	15-01-1997
		HU 9601808 A	28-04-1997
		JP 9071540 A	18-03-1997
		NO 962784 A	06-01-1997
		NZ 286920 A	24-06-1997
		US 5798375 A	25-08-1998
US 5663389 A	02-09-1997	IT 80950167 A	14-10-1996
		EP 0737681 A	16-10-1996
		JP 8291163 A	05-11-1996
US 5457109 A	10-10-1995	AU 678291 B	22-05-1997
		AU 7724994 A	03-04-1995
		CA 2168751 A	23-03-1995
		CN 1131391 A	18-09-1996
		CZ 9600722 A	16-10-1996
		EP 0719143 A	03-07-1996
		HU 75873 A	28-05-1997
		JP 9502722 T	18-03-1997
		NO 961052 A	14-03-1996
		SK 35196 A	10-12-1997
		WO 9507697 A	23-03-1995
		US 5602133 A	11-02-1997
		AU 1770997 A	29-05-1997
		AU 1771097 A	29-05-1997
		AU 679572 B	03-07-1997
		AU 7835194 A	03-04-1995
		CN 1134669 A	30-10-1996
		CZ 9600793 A	16-10-1996
		CZ 9602822 A	14-01-1998
		CZ 9602823 A	14-01-1998
		EP 0719140 A	03-07-1996
		FI 961213 A	14-05-1996
		HU 75874 A	28-05-1997
		JP 9502727 T	18-03-1997
		NO 961041 A	14-05-1996
		NZ 274346 A	24-06-1997
		WO 9507694 A	23-03-1995
		US 5478852 A	26-12-1995
US 5602133 A	11-02-1997	US 5457109 A	10-10-1995
		AU 678291 B	22-05-1997
		AU 7724994 A	03-04-1995
		CA 2168751 A	23-03-1995
		CN 1131391 A	18-09-1996
		CZ 9600722 A	16-10-1996
		EP 0719143 A	03-07-1996
		HU 75873 A	28-05-1997
		JP 9502722 T	18-03-1997
		NO 961052 A	14-03-1996
		SK 35196 A	10-12-1997
		WO 9507697 A	23-03-1995
		AU 1770997 A	29-05-1997
		AU 1771097 A	29-05-1997
		AU 679572 B	03-07-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/05178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5602133 A		AU 7835194 A	03-04-1995
		CN 1134669 A	30-10-1996
		CZ 9600793 A	16-10-1996
		CZ 9602822 A	14-01-1998
		CZ 9602823 A	14-01-1998
		EP 0719140 A	03-07-1996
		FI 961213 A	14-05-1996
		HU 75874 A	28-05-1997
		JP 9502727 T	18-03-1997
		NO 961041 A	14-05-1996
		NZ 274346 A	24-06-1997
		WO 9507694 A	23-03-1995
		US 5478852 A	26-12-1995